UCB, Inc. - 1950 Lake Park Drive, Smyrna, Georgia 30080

April 7, 2009

Roger Citron
State of Montana Medicaid

Dear Mr. Citron:

Your UCB, Inc. Representative Bobby White contacted the Medical Affairs Department with your request for information regarding Keppra XR™ (Levetiracetam Extended-Release). Thank you for letting us know how we can assist you.

Specifically, you requested:
• Information regarding overview (attached)
• Information regarding N01235 - Pivotal Study (attached)
• Information regarding bioequivalence (attached)
• Information regarding pharmacokinetics (attached)

Please review the enclosed Keppra XR™ (levetiracetam) extended-release tablets package insert for approved indications and complete prescribing information.

This material is provided in response to your specific request and may contain information that is not part of the FDA-approved product labeling. If you have additional questions or a patient has experienced an adverse event related to the abovementioned product(s), please contact us toll free at (866) 822-0068, option 9: Medical Information. We appreciate your interest in UCB, Inc., and in our products.

Sincerely,

Joanne Chia
Medical Information Specialist

US-JCH/JCC/4111

Enclosure(s):
Keppra XR™ Package Insert

Keppra XR™ (levetiracetam): Overview

SUMMARY:

- ***Indication***
  - Keppra XR™ (levetiracetam) extended-release tablets (LEV XR) is indicated as adjunctive therapy in the treatment of partial onset seizures (POS) in patients ≥ 16 years of age with epilepsy. [1]
- ***Availability:***
  - Keppra XR™ is currently available as 500mg and 750 mg tablets. [1]
- ***Dosing:***
  - Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg. [1]
- ***Efficacy:***
  - Keppra XR™ 1000mg tablets given once daily as add-on therapy in subjects with refractory epilepsy suffering from POS significantly reduced POS frequency over placebo (PBO) in patients uncontrolled on 1-3 AEDs. [2]
- ***Safety:***
  - Tolerability and safety of Keppra XR™ once daily was consistent with the known safety profile of Keppra® (levetiracetam) immediate-release tablets (LEV IR) twice daily. [2-7]
  - The incidence of TEAEs was similar between Keppra XR™ and PBO (53.2% Keppra XR™; 54.4% PBO). The most common adverse reactions (difference in incidence rate is ≥5% between Keppra XR™-treated patients and placebo-treated patients) were somnolence and irritability. [1-2]
- ***Pharmacokinetics:***
  - Bioavailability of Keppra XR™ tablets is similar to that of the Keppra® IR Tablets. [1]
  - Two 750 mg extended-release levetiracetam tablets were bioequivalent to a single administration of three 500 mg extended-release levetiracetam tablets. [1]
  - Keppra XR™ 2 X 500 mg given once daily result in bioequivalent C_{max} and AUC compared to a single dose to Keppra® 1 X 500mg immediate-release tablets given twice daily under fasting conditions. [4,7]

The package insert for Keppra XR™ (levetiracetam) extended-release tablets (LEV XR) contains more information. Please review the enclosed full prescribing information.[1]

Peltola *et al* (2008, Abstract) [2] **conducted Study N01235, a double-blind, placebo-controlled, randomized efficacy and safety study of Keppra XR™ (levetiracetam) extended release formulation (LEV XR), administered as 2x500 mg tablets once daily as add-on therapy in subjects (12-70 years) with refractory partial onset seizures that are uncontrolled on 1-3 AEDs**.

Patients were randomized (1:1) to receive once daily LEV XR 1000 mg (2 x 500 mg) or PBO. 158 (59 female, 99 males) patients were randomized to LEV XR (n=79) or PBO (n=79). Baseline characteristics were similar in both LEV XR and PBO groups.

Efficacy

The primary efficacy variable was the partial onset seizure (Type I) frequency per week over the 12- week Treatment Period. The median percent reduction in weekly partial onset seizure (Type I) frequency from Baseline over the Treatment Period was 46.1% in LEV XR group and 33.4% in PBO group. The estimated percent reduction over PBO in weekly partial onset seizure (Type I) frequency over the Treatment Period was statistically significant (14.4%; p = 0.038). 10% of this refractory patient population treated with LEV XR experienced freedom from POS throughout the treatment period (vs. 1.3% PBO).

Safety

Overall, the incidence of treatment-emergent adverse events (TEAEs) reported in the two treatment groups was similar (53.2% LEV XR; 54.4% PBO). The intensity of most of the TEAEs was mild to moderate.

The incidence of psychiatric / behavioral TEAEs (LEV XR 9.1%; PBO 10.1%) and seizure or epilepsy related TEAEs (LEV XR 2.6%; PBO 2.5%) were similar in both groups. The tolerability and safety of LEV XR was consistent with the known safety profile of Keppra®.

Table 1. Treatment-emergent AEs reported by ≥5% patients in either treatment group *(safety population; MedDRA preferred term)*

N (%)	QD	
	LEV XR 2×500 mg (N=77)	**PBO (N=79)**
Patients with ≥1 AE	41 (53.2)	43 (54.4)
Influenza	6 (7.8)	3 (3.8)
Somnolence	6 (7.8)	2 (2.5)
Headache	5 (6.5)	11 (13.9)
Nasopharyngitis	5 (6.5)	4 (5.1)
Irritability	5 (6.5)	0
Nausea	4 (5.2)	2 (2.5)
Dizziness	4 (5.2)	2 (2.5)

Rouits *et al* (2007, Abstract) [4,7] **compared the bioavailability and food effects of Keppra XR™ 2 X 500 mg (levetiracetam) extended-release tablets (LEV XR) given once daily (q.d.), with that of Keppra® 1 X 500 mg (levetiracetam) immediate-release (LEV IR) given twice daily (b.i.d.).**

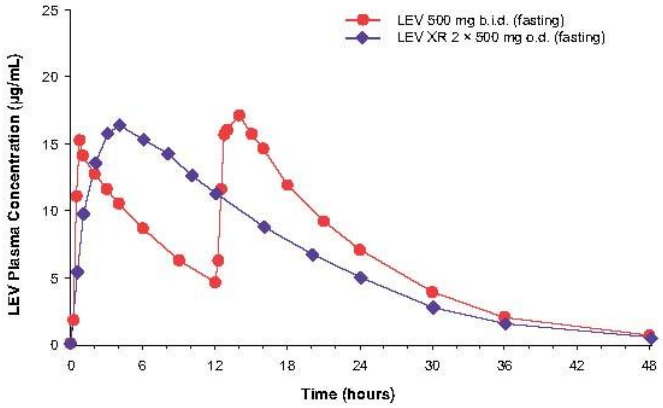
A Phase I, randomized, monocenter, open-label, three-way cross-over study was conducted in 24 healthy subjects (12 male, 12 female, aged 18-51 years). The treatment groups were: 1) LEV IR 500 mg given under fasting conditions on day 1 (single dose) and on days 3 to 9

(b.i.d.); 2) LEV XR 2 X 500 mg given under fasting conditions on day 1 (single dose) and on days 3 to 9 (q.d.) and 3) A single dose of LEV XR 2 X 500 mg given with a standard high-fat, high-calorie breakfast. Plasma drug concentrations were collected at various timepoints and these data were used to generate plasma concentration vs. time comparison profiles.

Table 2: Mean Pharmacokinetic Parameters and Bioequivalence Tests [4]

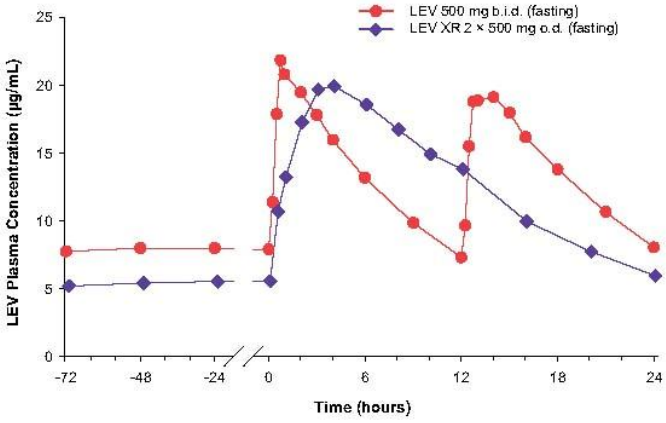
	Single Dose Bioavailability Comparison		**Steady-State Bioavailability Comparison**		**Food Effect Bioavailability Comparison**	
Parameter	LEV XR	LEV IR	LEV XR	LEV IR	LEV XR Fed	LEV XR Fasted
C_{max} (µg/mL)	17.4	19.7	21.3	25.6	19.5	17.4
t_{max} (h)	4	1	4	0.75	6	4

Figure 1: Single-Dose Bioavailability Comparison – Mean LEV Plasma Concentrations Following LEV XR 2 X 500 mg q.d. and LEV IR 500 mg b.i.d. [4]



In fasting state, single administration of LEV XR 2 X 500 mg q.d. was bioequivalent to the administration of LEV IR 1 X 500 mg b.i.d.

Figure 2: Steady-State Bioavailability Comparison – Mean Steady-State LEV Plasma Concentrations Following LEV XR 2 X 500 mg q.d. and LEV IR 500 mg b.i.d. [4]



After repeated dosing over one week, the AUC (extent of exposure) after LEV XR 2 X 500 mg q.d. was bioequivalent to LEV IR 1 X 500 mg b.i.d. At steady state, the time during which the plasma concentration of levetiracetam remained within 25% of maximum was 7.8 hours for LEV XR and 3.4 hours for LEV IR.

In this study, single and multiple doses of LEV IR 500 mg administered b.i.d., single and multiple doses of LEV XR 1000 mg administered q.d. in fasting conditions, and a single dose of LEV XR 1000 mg administered in fed conditions were safe and well tolerated in healthy male and female subjects.

REFERENCES:

1. Keppra XR™ [package insert]. Smyrna, GA: UCB; 2008.
2. Shorvon SD, Löwenthal A, Janz D, et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia 2000;41:1179−1186.
3. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000;55:236−242.
4. Rouits E, Burton I, Guénolé E, Troenaru M, Bendahmane S, Sargentini-Maier ML. Single- and multiple-dose bioequivalence and food effect comparison between levetiracetam extended release tablets once daily and levetiracetam immediate release tablets twice daily in healthy subjects [abstract]. Epilepsia 2007;48(Suppl 6):334.
5. Ben-Menachem E, Falter U, European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia. 2000;41:1276-1283.
6. Peltola J, Coetzee C, Jimenez F, Litovchenko T, Sridharan R et al. Once-Daily Extended Release Levetiracetam as Add-On Therapy in Patients with Refractory Partial-Onset Seizures: Double Blind, Placebo-Controlled Trial. Neurology 70: 2008. [Abstract].
7. UCB Inc., Data on file

Keppra XR™ (levetiracetam): Pivotal Study (N01235)

Summary:

- A prospective, randomized (1:1), double-blind, placebo-controlled, parallel group, multi-center efficacy and safety study of Keppra XR™ levetiracetam extended-release tablets (LEV XR) was conducted. [2]
- LEV XR 1000mg tablets were given once daily as add-on therapy without titration in subjects (12 to 70 years) with refractory epilepsy suffering from POS uncontrolled on 1-3 AEDs. [2]
- ***Primary Endpoint*** [2]
    - The median percent reduction in weekly partial onset seizure (POS) frequency from baseline over the treatment period was 46.1% in the LEV XR 1000 mg treatment group (N=74) and 33.4% in the placebo group (N=78).
    - The estimated percent reduction over placebo (14.4%) was statistically significant in weekly partial onset seizure frequency over the treatment period ($p = 0.038$).
- ***Secondary Endpoint(s)*** [2]
    - The proportion of 50%, 75% and 100% responders in POS (Type I) frequency per week over the Treatment Period were 43%, 24% and 10.1% (vs 29%, 11%, 1% for PBO)
- The incidence of TEAEs was similar between groups (53.2% LEV XR; 54.4% PBO). The most common adverse reactions (difference in incidence rate is ≥5% between Keppra XR™-treated patients and placebo-treated patients and occurred more frequently in Keppra XR™-treated patients) included: somnolence and irritability. [1,2]

The package insert for Keppra XR™ (levetiracetam) extended-release tablets contains information in the CLINICAL STUDIES (Section 14) section on this topic. Please review the enclosed full prescribing information.[1]

14 CLINICAL STUDIES

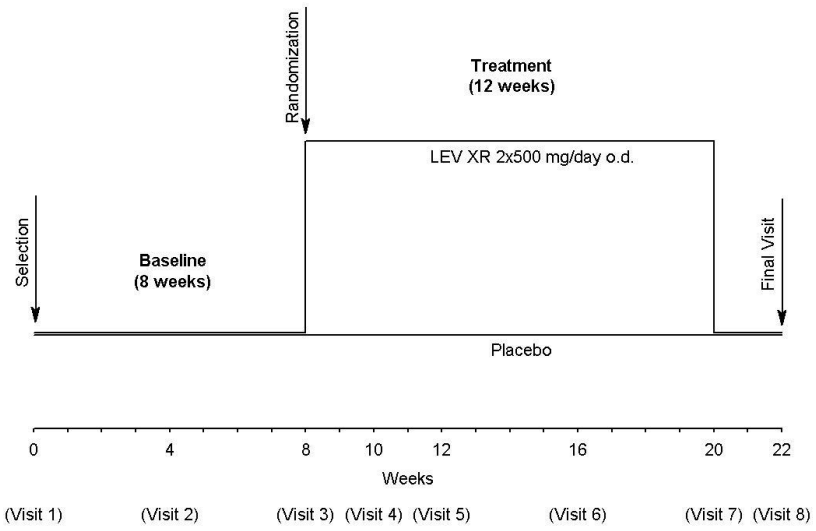
The effectiveness of KEPPRA XR as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization. Patients enrolled had at least eight partial seizures with or without secondary generalization during the 8-week baseline period and at least two partial seizures in each 4-week interval of the baseline period. Patients were taking a stable dose regimen of at least one and could take a maximum of three AEDs. After a prospective baseline period of 8 weeks, 158 patients were randomized to placebo (N=79) or KEPPRA XR (2x500 mg tablets) (N=79) given once daily over a 12-week treatment period.

The primary efficacy endpoint was the percent reduction over placebo in mean weekly frequency of partial onset seizures. The median percent reduction in weekly partial onset seizure frequency from baseline over the treatment period was 46.1% in the KEPPRA XR 1000 mg treatment group (N=74) and 33.4% in the placebo group (N=78). The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14.4% (statistically significant).

Peltola et al (2007, Abstract) [2-3] **conducted Study N01235, a double-blind, placebo-controlled, randomized efficacy and safety study of Keppra XR™ levetiracetam extended release formulation (LEV XR), administered as 2x500 mg tablets once daily as add-on therapy in subjects with refractory partial onset seizures that are uncontrolled on 1-3 AEDs**.

The study duration was 22 weeks, consisting of a 8-week Baseline Period followed by a 12-week Treatment Period with a Final Visit occurring within the two weeks after the last investigational drug intake for the subjects discontinuing prematurely or deciding to not convert to Keppra ® (levetiracetam immediate-release tablets) (LEV IR). Patients were randomized (1:1) to receive once daily LEV XR 1000 mg/day (2 x 500 mg) without titration or placebo (PBO). 158 (59 female, 99 males) patients were randomized to LEV XR (n=79) or PBO (n=79). This study was carried out in 7 countries: Brazil, Finland, India, Mexico, Russian Federation, South Africa, and Ukraine.

Figure 1: Study Diagram [3] UCB, Data on file



Inclusion/Exclusion Criteria

Eligible patients were between 12-70 years of age, weighed ≥50 kg, and had a confirmed diagnosis of POS for ≥ 6 months. Subjects must have had at least 8 POS with or without secondary generalization (Type IA, IB or IC according to the ILAE classification of epileptic seizures) during the 8-week prospective baseline period and at least two partial seizures in each 4-week interval of the Baseline Period. Patients were on a stable dose of 1-3 concomitant antiepileptic drugs (AEDs) for at least 4 weeks before the Selection Visit.

Primary Endpoint

The primary efficacy variable was the partial onset seizure (Type I) frequency per week over the 12- week Treatment Period. Similar results were seen for both ITT and PP populations.

The median percent reduction in weekly POS (Type I) frequency from Baseline over the Treatment Period was 46.1% in LEV XR treatment group and 33.4% in PBO group. The estimated percent reductions over PBO in weekly POS (Type I) frequency over the Treatment Period was 14.4% in the ITT population; this reduction over PBO was statistically significant (2-sided t-test, 5% significance level, p = 0.038).

Table 1: Primary Endpoint – Median percent reduction in weekly POS during baseline and over the 12-week treatment period. [2]

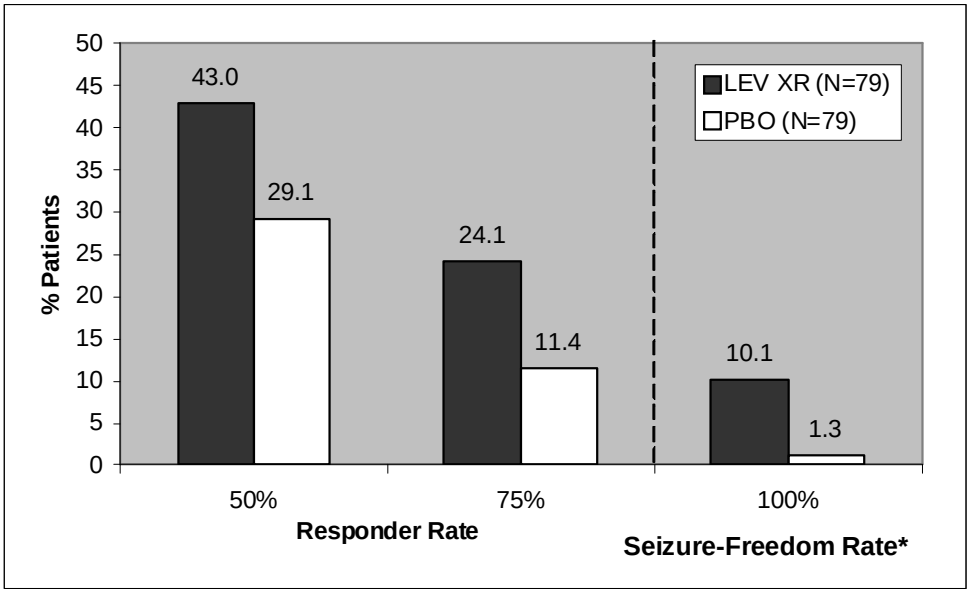
	Intent-to-treat (ITT) Population* **		**Per-Protocol (PP) Population**	
	LEV XR N = 79	**PBO N = 79**	**LEV XR N = 69**	**PBO N = 68**
% Reduction From Baseline				
- N	74	78	67	69
- Median	46.1	33.4	44.8	28.1
- (Q1-Q3)	(23.0−76.9)	(-6.6−51.8)	(23.0−73.9)	(-6.6−51.5)
% Reduction of LEV XR over PBO	14.4		18.6	
2-sided 95% CI (% Reduction)	0.9−26.0		6.7−28.9	
P value	0.038		0.003	

*** The ITT analysis is the Primary Efficacy Analysis

Secondary Endpoint(s)

- Categorized response in POS (Type I) seizure frequency/week from Baseline over the Treatment Period was grouped into five categories (percentage of patients with < -25%, - 25 to <25%, 25 to <75%, 75 to <100%, and 100% seizure frequency reduction). The categorized responses over the Treatment Period showed that more patients had positive responses after LEV XR compared to PBO. The distribution difference in categorized responses was statistically significant (p = 0.033).
- The proportion of 50%, 75% and 100% responders in POS (Type I) frequency per week over the Treatment Period is shown below.

Figure 2: 50% and 75% Responder Rates and Seizure Freedom Rates for POS *(ITT population)* [2]



*Only patients who completed the trial were counted as seizure free. 2/79 PBO (2.5%) patients had 100% response rate, but 1 terminated prematurely, therefore seizure freedom rate was 1.3% for PBO

Safety

Safety analyses were carried out on the safety population (n = 77 LEV XR, n = 70 PBO.) Overall, the incidence of treatment-emergent adverse events (TEAEs) reported in the two treatment groups was similar (53.2% LEV XR; 54.4% PBO). The intensity of most of the TEAEs was mild to moderate.

The most frequent TEAEs (incidence ≥5% within group) were as follows: headache (6.5% LEV XR vs 13.9% PBO), influenza (7.8% LEV XR vs 3.8% PBO), nasopharyngitis (6.5% LEV XR vs 5.1% PBO), somnolence (7.8% LEV XR vs 2.5% PBO), nausea (5.2% LEV XR vs 2.5% PBO), dizziness (5.2% LEV XR vs 2.5% PBO), and irritability (6.5% LEV XR vs 0 PBO). 9 treatment-emergent serious adverse events, including one death, were reported by 8 subjects (2 [2.5%] in the PBO group and 6 [7.8%] in the LEV XR group). One subject randomized to LEV XR died as a result of an acute respiratory failure due to pulmonary bronchiecteis. The event was considered by the Investigator as unlikely related to the study drug.

The incidence of psychiatric / behavioral TEAEs was similar in LEV XR (9.1%) and PBO (10.1%). One subject in the PBO group and none in the LEV XR group discontinued the study prematurely due to lack/loss of efficacy. The incidence of seizure or epilepsy related TEAEs was similar in LEV XR (2.6%) and PBO (2.5%). No clinically relevant changes from baseline were observed in ECG, vital signs, body weight, physicial and neurological exams. The tolerability and safety of LEV XR was consistent with that known safety profile of Keppra®.

Table 2: Treatment-emergent AEs reported by ≥5% patients in either treatment group *(safety population; MedDRA preferred term)* [2]

N (%)	QD	
	LEV XR 2×500 mg (N=77)	**PBO (N=79)**
Patients with ≥1 AE	41 (53.2)	43 (54.4)
Influenza	6 (7.8)	3 (3.8)
Somnolence	6 (7.8)	2 (2.5)
Headache	5 (6.5)	11 (13.9)
Nasopharyngitis	5 (6.5)	4 (5.1)
Irritability	5 (6.5)	0
Nausea	4 (5.2)	2 (2.5)
Dizziness	4 (5.2)	2 (2.5)

Trial Completion

143 subjects (n = 72 PBO; n = 71 LEV XR) completed the study. 139 subjects (n = 72 PBO; n = 67 LEV XR) decided to continue in the N01245 Named Patient Program or switched to prescription Keppra® levetiracetam immediate release tablets.

Conclusions

This study demonstrates that LEV XR administered 2 x 500 mg once daily during a 12-week treatment period was effective, safe and well tolerated in subjects from 12 to 70 years of age with refractory epilepsy suffering from POS.

References:

1. Keppra XR™ [package insert]. Smyrna, GA: UCB; 2008.
2. Peltola J, Coetzee C, Jimenez F, Litovchenko T, Sridharan R et al. Once-Daily Extended Release Levetiracetam as Add-On Therapy in Patients with Refractory Partial-Onset Seizures: Double Blind, Placebo-Controlled Trial. Neurology 70: 2008. [Abstract].
3. UCB Inc., Data on File. N01235

Keppra XR™ (levetiracetam): Bioequivalence

SUMMARY:

- Bioavailability of Keppra XR™ (levetiracetam extended-release tablets) is similar to that of the Keppra® (levetiracetam immediate-release tablets). [1]
- Keppra XR™ 2 X 500 mg given once daily result in bioequivalent C_{max} and AUC compared to a single dose to Keppra® 1 X 500mg given twice daily. [2]
- Two 750 mg extended-release levetiracetam tablets were bioequivalent to a single administration of three 500 mg extended-release levetiracetam tablets. [1]
- The time to peak plasma concentrations is about 3 hours longer with Keppra XR™ than with Keppra®. [1]
- *Single dose*
    - Single administration of two 500 mg Keppra XR™ tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentration versus time as did the administration of one 500 mg Keppra® tablet twice daily in fasting conditions. [1]
- *Multiple doses*
    - After multiple dose Keppra XR™ tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose Keppra® tablets intake. [1]
    - At steady state, the time during which the plasma concentration of levetiracetam remained within 25% of maximum was 7.8 hours for LEV XR and 3.4 hours for LEV IR. [3]
    - C_{max} and C_{min} were lower by 17% and 26% after multiple dose Keppra XR™ tablets intake in comparison to multiple dose Keppra® tablets intake. [1]

The package insert for Keppra XR™ (levetiracetam extended-release tablets) contains information in the CLINICAL PHARMACOLOGY (Section 12) on this topic. Please review the enclosed full prescribing information.[1]

12 CLINICAL PHARMACOLOGY

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12.3 Pharmacokinetics

Overview

Bioavailability of Keppra XR tablets is similar to that of the Keppra IR Tablets. The pharmacokinetics (AUC and Cmax) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended-release levetiracetam. Plasma half-life of extended-release levetiracetam is approximately 7 hours.

<..>

Absorption and Distribution

Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam than with immediate-release tablets.

Single administration of two 500 mg extended-release levetiracetam tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentration versus time as did the administration of one 500 mg immediate-release tablet twice daily in fasting conditions. After multiple dose extended-release levetiracetam tablets intake, extent of exposure (AUC0-24) was similar to extent of exposure after multiple dose immediate-release tablets intake. Cmax and Cmin were lower by 17% and 26% after multiple

dose extended-release levetiracetam tablets intake in comparison to multiple dose immediate-release tablets intake. Intake of a high fat, high calorie breakfast before the administration of extended-release levetiracetam tablets resulted in a higher peak concentration, and longer median time to peak. The median time to peak (Tmax) was 2 hours longer in the fed state.

Two 750 mg extended-release levetiracetam tablets were bioequivalent to a single administration of three 500 mg extended-release levetiracetam tablets.
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14 CLINICAL STUDIES
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The relationship between the effectiveness of the same daily dose of KEPPRA XR and immediate-release KEPPRA has not been studied and is unknown.

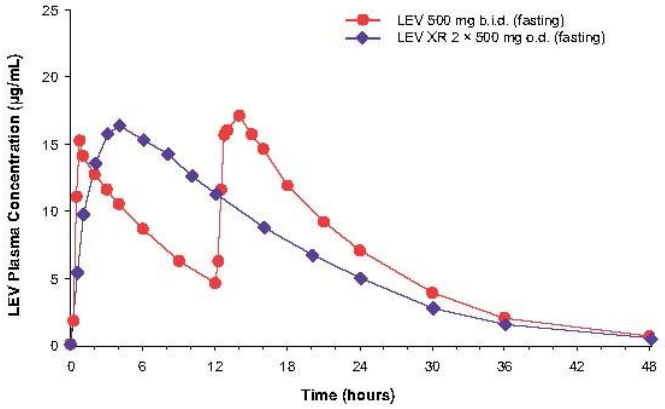
Rouits *et al* (2007, Abstract) and Data on File N01160 [2-3] **compared the bioavailability and food effects of Keppra XR™ 2 X 500mg (levetiracetam extended-release tablets; LEV XR) given once daily (q.d.), with that of Keppra® 1 X 500mg (levetiracetam immediate-release tablets; LEV IR) given twice daily (b.i.d.).**

A Phase I, randomized, monocenter, open-label, three-way cross-over study was conducted in 24 healthy subjects (12 male, 12 female, aged 18-51 years). The treatment groups were: 1) LEV IR 500mg given under fasting conditions on day 1 (single dose) and on days 3 to 9 (b.i.d.); 2) LEV XR 2 X 500mg given under fasting conditions on day 1 (single dose) and on days 3 to 9 (q.d.) and 3) A single dose of LEV XR 2 X 500mg given with a standard high-fat, high-calorie breakfast. Plasma drug concentrations were collected at various timepoints and these data were used to generate plasma concentration vs. time comparison profiles.

Table 1: Mean Pharmacokinetic Parameters and Bioequilvalence Tests [2]

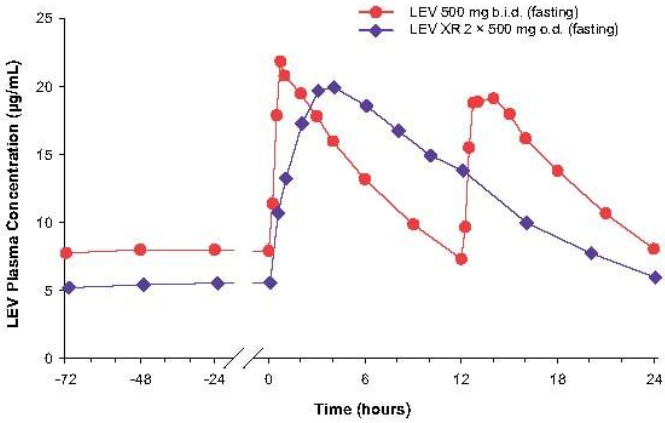
	Single Dose Bioavailability Comparison		**Steady-State Bioavailability Comparison**		**Food Effect Bioavailability Comparison**	
Parameter	LEV XR	LEV IR	LEV XR	LEV IR	LEV XR Fed	LEV XR Fasted
C_{max} (µg/mL)	17.4	19.7	21.3	25.6	19.5	17.4
t_{max} (h)	4	1	4	0.75	6	4
AUC∞, ug·h/mL	313	325	-	-	298	313
AUC_{24h}, µg·h/mL	-	-	309	327	-	-

Figure 1: Single-Dose Bioavailability Comparison – Mean LEV Plasma Concentrations Following LEV XR 2 X 500 mg q.d. and LEV IR 500 mg b.i.d. [2]



In fasting state, single administration of LEV XR 2 X 500mg q.d. was bioequivalent to the administration of LEV IR 1 X 500mg b.i.d.

Figure 2: Steady-State Bioavailability Comparison – Mean Steady-State LEV Plasma Concentrations Following LEV XR 2 X 500mg q.d. and LEV IR 500mg b.i.d. [2]



After repeated dosing over one week, the AUC (extent of exposure) after LEV XR 2 X 500mg q.d. was bioequivalent to LEV IR 1 X 500mg b.i.d. At steady state, the time during which the plasma concentration of levetiracetam remained within 25% of maximum was 7.8 hours for LEV XR and 3.4 hours for LEV IR.

Twenty subjects reported at least 1 treatment-emergent adverse event (TEAE). All adverse events (AEs) were mild or moderate in intensity and resolved during the study. The most frequent AEs assessed as drug-related were: asthenia (17 subjects), somnolence (5 subjects), nightmare (4 subjects), disturbance in attention (3 subjects), insomnia (2 subjects), and headache (2 subjects). None of the AEs led to treatment discontinuation. One subject had blood and leukocytes in urine, which was related to burning micturition and pollakiuria. The

TEAEs of this 1 subject were deemed unlikely to be related to the study treatment by the investigator.

Drug related adverse events occurred in 54% and 71% of Keppra XR™ and Keppra® IR patients, respectively; those occurring in patients taking Keppra XR™ did not differ from the known tolerability profile of Keppra®.

In this study, single and multiple doses of LEV IR 500 mg administered b.i.d., single and multiple doses of LEV XR 1000 mg administered q.d. in fasting conditions, and a single dose of LEV XR 1000 mg administered in fed conditions were safe and well tolerated in healthy male and female subjects.

REFERENCES:

1. Keppra XR™ [package insert]. Smyrna, GA: UCB; 2008.
2. Rouits E, Burton I, Guénolé E, Troenaru M, Bendahmane S, Sargentini-Maier ML. Single- and multiple-dose bioequivalence and food effect comparison between levetiracetam extended release tablets once daily and levetiracetam immediate release tablets twice daily in healthy subjects [abstract]. Epilepsia 2007;48(Suppl 6):334.
3. UCB Inc., Data on File. N01160

Keppra XR™ (levetiracetam): Pharmacokinetics

SUMMARY:

- A randomized open-label dose-proportionality study has been completed, demonstrating that the pharmacokinetics of Keppra XR™ 500mg (levetiracetam) extended-release tablets (LEV XR) are dose-proportional in the range of 1000 to 3000mg per intake. [2]
- The rate (C_{max}) and extent of absorption (AUC) were found to be dose-proportional, while $t_{½}$, CL/F and V_z/F was dose-independent. [2]
- Bioavailability of Keppra XR™ tablets is similar to that of the Keppra® (levetiracetam) immediate-release tablets (LEV IR). [1]
- Two 750 mg extended-release levetiracetam tablets were bioequivalent to a single administration of three 500 mg extended-release levetiracetam tablets. [1]
- LEV XR 2 X 500 mg given once daily result in bioequivalent C_{max} and AUC compared to a single dose to LEV IR 1 X 500mg given twice daily under fasting conditions. [3]
- At steady state, the time during which the plasma concentration of levetiracetam remained within 25% of maximum was 7.8 hours for LEV XR and 3.4 hours for LEV IR. [4]
- The rate and extent of absorption of the LEV XR 500 mg tablets were not modified by intake with a standardized high-fat breakfast. The median time to peak (T_{max}) was 2 hours longer in the fed state. LEV XR can be taken with or without food. [1,3]
- Population pharmacokinetics has been studied in healthy volunteers and epilepsy patients with partial onset seizures to identify pharmacokinetic parameters. [4]

The package insert for Keppra XR™ (levetiracetam) extended-release tablets (LEV XR) contains information in the CLINICAL PHARMACOLOGY (Section 12) on this topic. Please review the enclosed full prescribing information. [1]

Prospective Studies

Data on File N01260 [2] **conducted a Phase I, randomized, monocenter, open-label, three-way cross-over dose proportionality study of Keppra XR™ (levetiracetam) extended-release tablets (LEV XR) 500mg in 24 healthy male and female volunteers.**

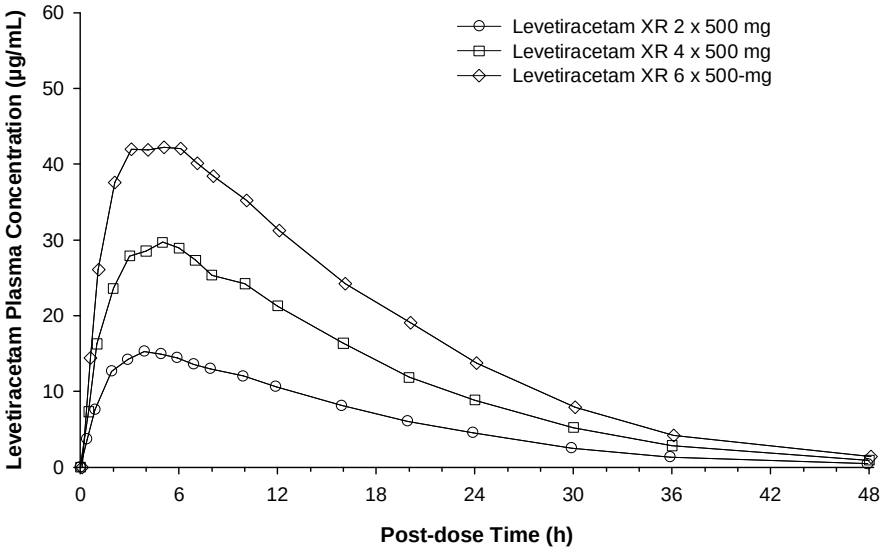
The primary objective of this study was to compare the single dose bioavailability of varying doses of LEV XR 500mg. Under fasting conditions, subjects received a single dose of either two (1000mg), four (2000mg), or six (3000mg) of LEV XR 500mg tablets. The rate (C_{max}) and extent of absorption (AUC) were found to be dose-proportional, while $t_{½}$, CL/F and V_z/F were dose-independent.

Table 1: Pharmacokinetics of Keppra XR ™ 500 mg tablets [2]

Parameter (N=24)	Keppra XR™ (levetiracetam) dose		
	2 x 500 mg	4 x 500 mg	6 x 500 mg
C_{max} (µg/mL)	16.2	31.5	46.2
t_{max} (h)	4.50	5.00	4.50
AUC(0-t) (µg.h/mL)	280	559	839
AUC (µg.h/mL)	285	570	855
$t_{½}$ (h)	7.26	7.33	7.15
CL/F (mL/min)	58.4	58.5	58.5
V_z/F (L)	36.7	37.1	36.2

Plasma concentration of LEV XR was measured in all subjects at various time-points up to 48 h after the single dose administration with LEV XR 2 x, 4 x, or 6 x 500mg tablets.

Figure 1: Geometric mean concentration profile of single-dose administration of Keppra XR™ 2 X, 4X or 6 X 500mg tablets [2]



The most frequently reported TEAEs were: somnolence (9 subjects), asthenia (7 subjects), dizziness (4 subjects), muscle spasms (3 subjects), and rhinitis (3 subjects). All reported adverse events (AEs) were mild to moderate in intensity and none of the reported AEs led to treatment discontinuation. No clinically relevant changes in vital signs, physical examination

and ECG data were observed. The single dose pharmacokinetics of LEV XR is dose-proportional in the 1000 to 3000 mg range.

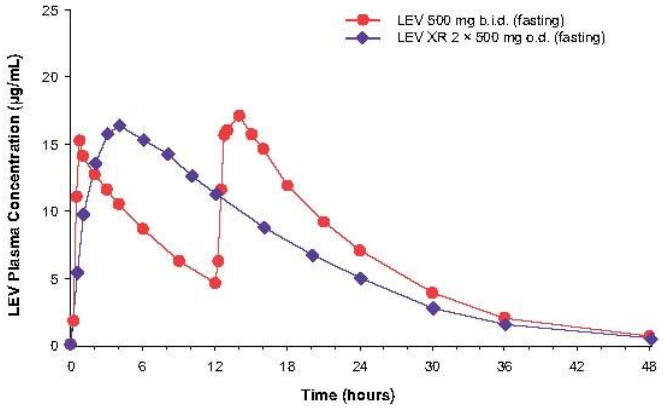
Rouits *et al* (2007, Abstract) and Data on File N01160 [3-4] **compared the bioavailability and food effects of Keppra XR™ 2 X 500mg (levetiracetam) extended-release tablets (LEV XR) given once daily (q.d.), with that of Keppra® 1 X 500mg (levetiracetam) immediate-release tablets (LEV IR) given twice daily (b.i.d.).**

A Phase I, randomized, monocenter, open-label, three-way cross-over study was conducted in 24 healthy subjects (12 male, 12 female, aged 18-51 years). The treatment groups were: 1) LEV IR 500mg given under fasting conditions on day 1 (single dose) and on days 3 to 9 (b.i.d.); 2) LEV XR 2 X 500mg given under fasting conditions on day 1 (single dose) and on days 3 to 9 (q.d.) and 3) A single dose of LEV XR 2 X 500mg given with a standard high-fat, high-calorie breakfast. Plasma drug concentrations were collected at various timepoints and these data were used to generate plasma concentration vs. time comparison profiles.

Table 2: Mean Pharmacokinetic Parameters and Bioequilvalence Tests [3]

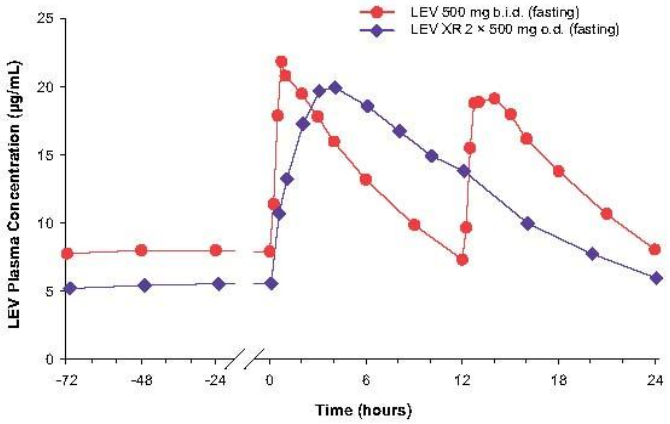
	Single Dose Bioavailability Comparison		**Steady-State Bioavailability Comparison**		**Food Effect Bioavailability Comparison**	
Parameter	LEV XR	LEV IR	LEV XR	LEV IR	LEV XR Fed	LEV XR Fasted
C_{max} (µg/mL)	17.4	19.7	21.3	25.6	19.5	17.4
t_{max} (h)	4	1	4	0.75	6	4

Figure 2: Single-Dose Bioavailability Comparison – Mean LEV Plasma Concentrations Following LEV XR 2 X 500 mg q.d. and LEV IR 500 mg b.i.d. [3]



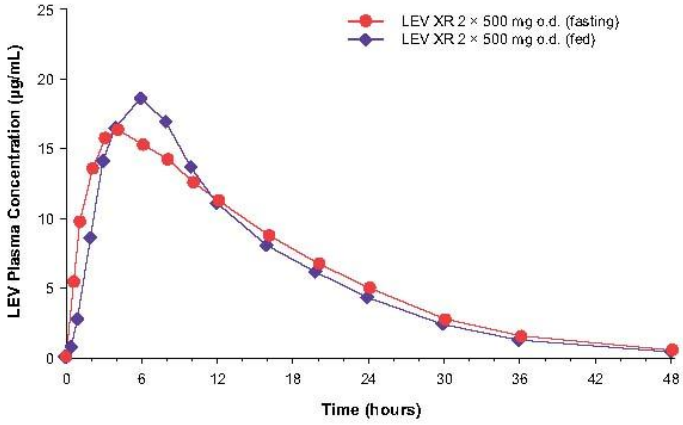
In fasting state, single administration of LEV XR 2 X 500mg q.d. was bioequivalent to the administration of LEV IR 1 X 500mg b.i.d.

Figure 3: Steady-State Bioavailability Comparison – Mean Steady-State LEV Plasma Concentrations Following LEV XR 2 X 500mg q.d. and LEV IR 500mg b.i.d. [3]



After repeated dosing over one week, the AUC (extent of exposure) after LEV XR 2 X 500mg q.d. was bioequivalent to LEV IR 1 X 500mg b.i.d. At steady state, the time during which the plasma concentration of levetiracetam remained within 25% of maximum was 7.8 hours for LEV XR and 3.4 hours for LEV IR.

Figure 4: Food Effect – Mean LEV Plasma Concentrations Following Intake of LEV XR 2 X 500mg After an Overnight Fast or With a High-Fat Breakfast [3]



Food intake did not modify the pharmacokinetics of the LEV XR formulation in a clinically relevant way. Following a high-fat meal, time-to-peak was delayed with LEV XR, although C_{max} and AUC ratios were within bioequivalence limits

Drug related adverse events occurred in 54% and 71% of LEV XR and LEV IR patients, respectively; those occurring in patients taking LEV XR did not differ from the known tolerability profile of LEV IR.

In this study, single and multiple doses of LEV IR 500 mg administered b.i.d., single and multiple doses of LEV XR 1000 mg administered q.d. in fasting conditions, and a single dose

of LEV XR 1000 mg administered in fed conditions were safe and well tolerated in healthy male and female subjects.

Pharmacokinetic Modeling Study

Data on File N01286 [5] **characterized the pharmacokinetics of Keppra XR™ 500 mg (levetiracetam) extended-release tablets (LEV XR) in healthy subjects and in epilepsy patients with partial onset seizures, to identify factors affecting pharmacokinetic parameters, and to simulate scenarios of non-compliance.**

Concentration-time profile data was collected following a single dose (fed and fasted) and multiple dose administration of (i) LEV XR or LEV IR in healthy volunteers and of (ii) LEV XR in epileptic patients with partial onset seizures. The structural model for data analysis was a one-compartment pharmacokinetic model. The typical first order absorption rate constant was about 20-fold lower for LEV XR than for LEV IR, and it was only slightly reduced by a high fat meal. The apparent clearance (0.95 mL/min/kg) and Vd (0.6 L/kg) for the typical individual were consistent with Keppra® IR pharmacokinetics.

Deviations from the planned dosing schedule were simulated as non-compliance scenarios (missing dose, dose taken late, missing dose followed by double rescue dose the day after). The model predicts that the return to the initial C_{max} and C_{trough} takes place within 24 hours. Patients taking LEV XR 1000mg once daily appeared to be adequately exposed with predicted C_{max} and C_{trough} in the range of those observed after LEV IR 500mg twice daily dosing

REFERENCES:

1. Keppra XR™ [package insert]. Smyrna, GA: UCB; 2008.
2. UCB Inc., Data on File. N01260
3. Rouits E, Burton I, Guénolé E, Troenaru M, Bendahmane S, Sargentini-Maier ML. Single- and multiple-dose bioequivalence and food effect comparison between levetiracetam extended release tablets once daily and levetiracetam immediate release tablets twice daily in healthy subjects [abstract]. Epilepsia 2007;48(Suppl 6):334.
4. UCB Inc., Data on File. N01160
5. UCB Inc., Data on File. N01286